

Diaretinopathy database –A Gene database for diabetic retinopathy

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Abstract:

Diabetic retinopathy, is a microvascular complication of diabetes mellitus and is a major cause of adult blindness. Despite advances in diagnosis and treatment the pathogenesis of diabetic retinopathy is not well understood. Results from epidemiological studies of diabetic patients suggest that there are familial predispositions to diabetes and to diabetic retinopathy. Therefore the main purpose of this database is to help both scientists and doctors in studying the candidate genes responsible for causing diabetic retinopathy. For each candidate gene official symbol, chromosome map, number of exons, GT-AG introns, motif, polymorphic variation and 3D structure are given respectively. In addition to molecular class and function of these genes, this database also provides links to download the corresponding nucleotide and amino acid sequences in FASTA format which may be further used for computational approaches. Therefore this database will increase the understanding of the genetics underlying the development or progression of diabetic retinopathy and will have an impact on future diagnostic, prevention and intervention strategies.

Availability: The database is freely available at <http://diaretinopathydatabase.com>

Key Words: Diabetic Retinopathy, Genes, SORD, ACE, VEGF, AGTR1

Background:

Diabetic retinopathy, a microvascular complication of diabetes mellitus is a major cause of non-inherited blindness among adults [1]. It is the second leading cause of blindness due to retinal degeneration in the working age group, contributing to an overall 4.8 % blindness across the globe [2]. India, being the diabetic capital of the world, is feared to end up with an alarming 11.4 million type 2 diabetes mellitus individuals developing this sight threatening disease by 2025 if the present trend of 20 % type 2 diabetes mellitus population developing diabetic retinopathy were to continue [3]. Although diabetic retinopathy is a common complication of diabetes, we still know little about the underlying molecular mechanisms. Analyzing the molecular aspects that govern the development of a disease or predisposition to a disease would achieve

desirable clinical outcomes by helping physicians to decide specific management of the disease depending upon the patient's genetic and environmental profile rather than a generalized treatment as laser photocoagulation [4]. Moreover, recognizing an underlying genetic susceptibility would help in counseling presymptomatic individuals to adopt preventive and control measures to delay the onset of disease. Therefore this database will help the scientists and doctors in studying the candidate genes responsible for causing diabetic retinopathy and progress faster the diagnostic treatment.

Methodology:

It is found through Literature survey and analysis that many genes play an imperative role in causing the disease. Information on those genes which play active role in diabetic

retinopathy was retrieved from NCBI (National Center for Biotechnology Information) database. The data were normalized to reduce and eliminate redundancy. The protein functional information was extracted from UniProt database which is curated manually. The structures of proteins were extracted from PDB (Protein Data Bank) which is a world-wide repository of information about the three dimensional structures of large biological molecules.

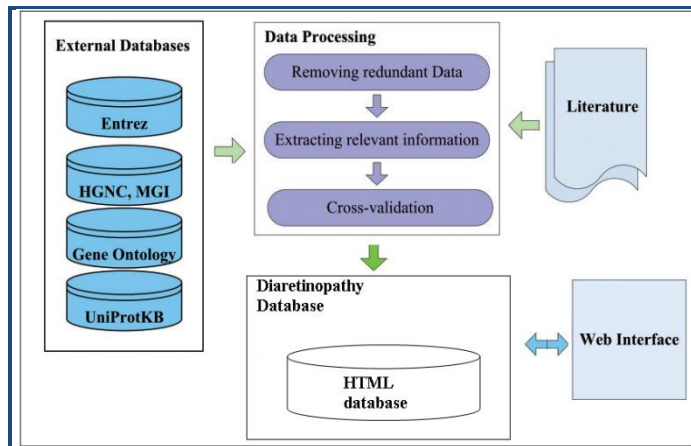


Figure 1: The Schema of data collection for Diaretinopathy database

Data collection:

Data for this novel database were collected from various literature sources such as PubMed [5], Science Direct [6], Biomed Central [7], Springer link [8], Scirus [9], Wiley journals [10] and also from specific Diabetic journals. The data is provided in alphabetical order and the records are organized to simplify the task of finding any relevant gene. The schema of data collection is given in Figure 1. The database can be accessed alphabetically either using gene name or alternative names for detailed information of the gene.

Construction of Diaretinopathy database:

The Diaretinopathy database is a HTML based database and is represented in table format. The home page and the gene page of this database is given as screenshot in Figure 2 and 3. The database is freely available to view and download data at <http://diaretinopathydatabase.com/>.

Database features:

Diaretinopathy database acts as complete web source providing information of 102 potential candidate genes Table 1 (see supplementary material) causing diabetic retinopathy at molecular, biochemical and at structural level. For each candidate genes the database is designed by taking 24 parameters into consideration that comprises official Symbol, alternative names, description, chromosome map showing the location, number of exons and GT-AG introns, motif, polymorphic variation, Enzyme commission (EC) number, catalytic activity, active site, cofactor, biophysicochemical properties, enzyme regulation, induction, molecular pathway, interactors, post translational modification, and 3D structure. In addition to the molecular class and function of these genes, this database also provides links to download the corresponding nucleotide and aminoacid sequences in FASTA format from NCBI and UNIPROT database respectively which may further be used for their computational approaches.

Software:

Microsoft windows 95/98/2000/2003/XP operating system was used in the development. HTML was used for the creation of web pages and Javascript was used for the development of database front end.

Hardware:

Personal computer with high speed processor with windows 95/98/2000/XP Os was used. We used 10.08 MB memory for running the database.

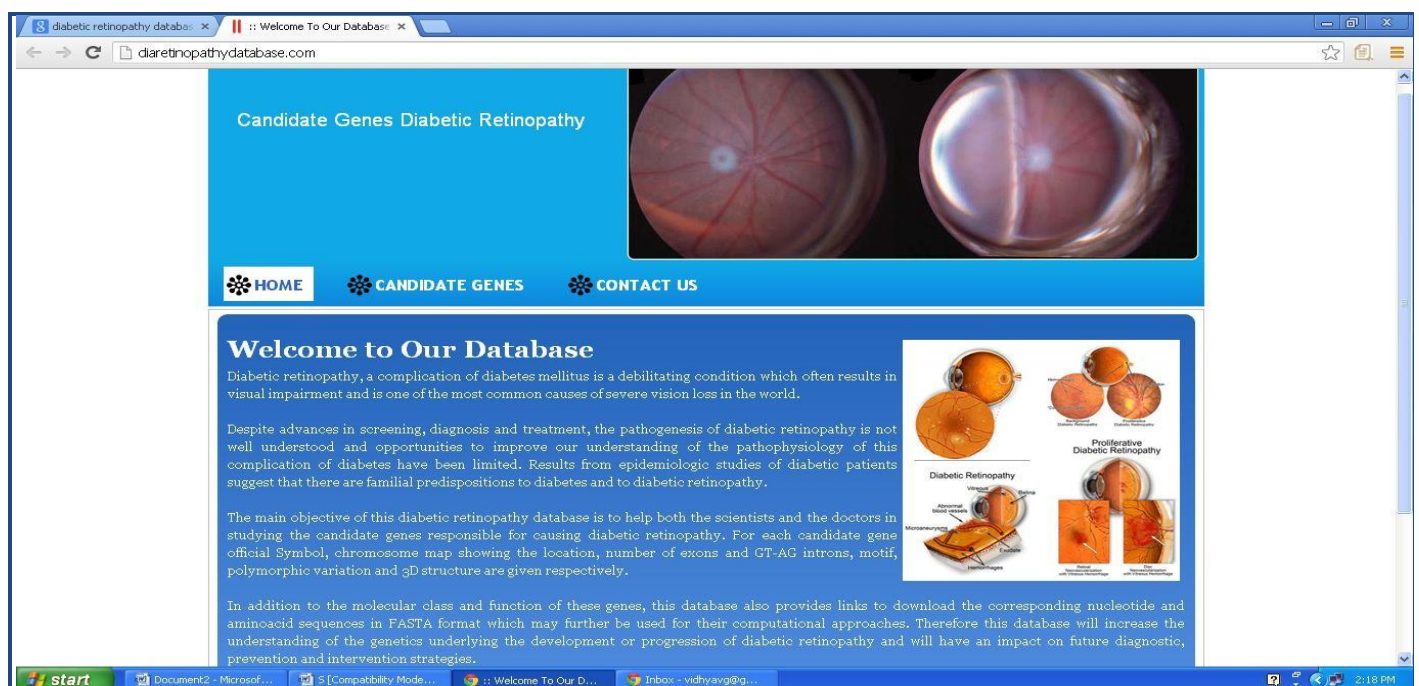


Figure 2: A Screenshot of the database "DIARETINOPATHY DATABASE" home page with links.

ACE	Angiotensin I Converting Enzyme
ADIPQO	
AGER	
AGT	
AGTR1	
AKR1B1	
AKR1B10	
AKT3	
ANGPT2	
ADLN	
ADLNR	
APOA1	
ARHGAP22	
Official Symbol	ACE
Alternative Names	Peptidase P, Kininase II, Carboxycathepsin, Dipeptidyl carboxypeptidase 1
Description	This gene encodes an enzyme exopeptidase involved in catalyzing the conversion of angiotensin I into a physiologically active peptide angiotensin II. Angiotensin II is a potent vasopressor and aldosterone-stimulating peptide that controls blood pressure and fluid-electrolyte balance. This enzyme plays a key role in the renin-angiotensin system. Many studies have associated the presence or absence of a 287 bp Alu repeat element in this gene with the levels of circulating enzyme or cardiovascular pathophysiology. Multiple alternatively spliced transcript variants encoding different isoforms have been identified, and two most abundant, spliced variants encode the somatic form and the testicular form, respectively, that are equally active.
Location	17q23.3
Map	<p>Chr 17</p> <p>Start: 61,554,432 bp from pter End: 61,599,209 bp from pter Size: 44,778 bases Orientation: plus strand</p>
Exons and Introns	26 exons and 58 distinct introns (54 gt-ag, 3 gc-ag, 1 other).
Nucleotide Sequence	Click Here to see the Sequence
Aminoacid Sequence	Click Here to see the Sequence
Variation	rs4343 A/G
Motif	Pfam: Peptidase_M2 PROSITE: Zinc_Protease
Ec No.	3.4.16.1
Catalytic Activity	Release of a C-terminal dipeptide, oligopeptide-I-Xaa-Yaa, when Xaa is not Pro, and Yaa is neither Asp nor Glu. Thus, conversion of angiotensin I to angiotensin II, with increase in vasoconstrictor activity, but no action on angiotensin II.
Active Site	Zinc binding motif HEXXH
Cofactor	Binds 3 chloride ions per subunit Binds 2 zinc ions per subunit
Biophysico chemical Properties	Kinetic parameters: KM=2.51 mM for Hip-His-Leu
Enzyme Regulation	Strongly activated by chloride. Specifically inhibited by lisinopril, captopril and enalaprilat
Induction	Up-regulated in failing heart
Pathway	<p>ACE inhibitor pathway</p> <p>Renin-Angiotensin-Aldosterone-System-acting drug pathway (PD)</p>
Interactors	Protein interactors Bradykinin receptor 2 Catechol -O-, methyltransferase Angiotensin II receptor 2 Non protein interactors Zinc
Post Translational Modification	Phosphorylated by CK2 on Ser-1299, which allows membrane retention
Molecular Weight	149714 da
Molecular Class	Enzyme: Hydrolase
Molecular Function	Actin binding Bradykinin receptor binding Carboxypeptidase activity Chloride ion binding Drug binding Metallopeptidase activity Zinc ion binding Converts angiotensin I to angiotensin II by release of the terminal His-Leu, this results in an increase of the vasoconstrictor activity of angiotensin. A Has also a glycosidase activity which releases GPI-anchored proteins from the membrane by cleaving the mannose linkage in the GPI moiety
3D Structure	

Figure 3: A Screenshot of the Gene page in DIARETINOAPHTHY DATABASE

Utility

This is however, the first database containing information of susceptibility genes causing diabetic retinopathy. This database finds utility to the scientific community for a quick review on the genetic basis of disease and may serve as a platform for therapeutic treatments.

Future development:

The database will be updated periodically and will be linked to related resources in near future for easy accessing of information so as to ensure that users get latest information on diabetic retinopathy. Additionally, our next prospective goal is to provide drugs that are used in the treatment of diabetic retinopathy treatment.

Acknowledgement:

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Supplementary material:

Table 1: Overview of list of genes in DIARETINOPATHY DATABASE

Candidate Genes	Location	Function
ACE	17q23.3	Metallopeptidase activity
ADIPOQ	3q27	Angiogenesis
AGER	6p21.3	Inflammation
AGT	1q42.2	Vasoconstrictor
AGTR1	3q24	Transducer
AKR1B1	7q35	Catalytic activity
AKR1B10	7q33	Detoxification of reactive aldehydes
AKT3	1q44	Cell survival
ANGPT2	8p23.1	Antagonist
APLN	Xq25	Homeostasis
APLNR	11q12	Transducer
APOA1	11q23-q24	Cofactor
AGHGAP 22	10q11.22	angiogenesis.
B4GALT2	1p34-p33	Galactosyltransferase activity
BMP4	14q22-q23	Cartilage and bone formation
CCDC68	8q21	Unknown
CCL2	17q11.2-q12	Chemotactic factor
CCNL1	3q25.31	Transcription regulator
CORT	1p36.22	Neuropeptide
CREB5	7p15.1	Activates transcription
CRP	1q21-q23	Host defense
CTGF	6q23.1	Chondrocyte proliferation and differentiation,
EDN1	6p24.1	Vasoconstrictor
ENG	9q33-q34.1	Binding of endothelial cells to integrins
ENO2	12p13	Catalytic activity
EPO	7q22	Erythroid differentiation
FABP2	4q28-q31	Lipid sensor
FGF2	4q26	Neurotrophic factor
GDNF	5p13.1-p12	Growth factor
GRAMD3	5q23.2	Unknown
GSTM1	1p13.3	Detoxification
H1F1A	14q23.2	Embryonic vascularization
HP	16q22.2	
HS6ST3	13q32.1	Catalytic activity
ICAM1	19p13.3-p13.2	
IGF1	12q23.2	Mammalian growth and development
IGSF21	1p36.13	Unknown
IL6	7p21	Immunoregulatory function
INSR	19p13.3-p13.2	Tyrosine-protein kinase activity.
IRF8	16q24.1	Transcription factor
ITGA2	5q11.2	
KCNK1	1q42-q43	Potassium rectifier channel
KIAA0825	5q15	Unknown
KIAA1804	1q42	Unknown
KIT	4q11-q12	Mast cell growth factor
KITLG	12q22	Mediates cell-cell adhesion
KLHDC7A	1p36.13	Cytoskeletal associated protein
LEKR1	3q25.31	Unknown
LIPG	18q21.1	Binds heparin
MAPK3	16p11.2	Regulation of postmitotic functions
MME	3q25.1-q25.2	Hydrolase activity
MMP2	16q13-q21	Cell proliferation
MMP9	20q11.2-q13.1	Angiogenesis
MPRIP	17p11.2	Cytoskeleton
MRPS15	1p34.3	Ribonucleoprotein
MTHFR	1p36.3	Catalytic activity

MYSM1	1p32.1	Chromatin regulator
MYT1L	2p25.3	Cns developmental protein
NFKB1	4q24	Pleiotropic transcription factor
NOS3	7q36	Reactive free radical
ODZ2	5q34	Transcription regulator activity
OSCP1	1p34.3	Involved in drug clearance in the placenta
PGF	14q24.3	Mitogen growth factor
PLXDC1	17q21.1	Endothelial cell capillary morphogenesis
PLXDC2	10p12.31	tumor angiogenesis
PON1	10p12.31	protect against development of atherosclerosis
POSTN	13q13.3	Cell adhesion.
PPARG	3p25	Key regulator of adipocyte differentiation
PRKCB	16p11.2	Chromatin regulator
PRKCD	3p21.31	Tumor promoter
PRL	6p22.2-p21.3	promotes lactation
PTGS2	1q25.2-q25.3	Inflammation
RBF0X1	16p13.3	
RBP4	10q23-q24	Cargo protein
ROBO4	11q24.2	Developmental protein
ROCK2	2p24	Centrosome duplication
SELE	1q22-q25	Capillary morphogenesis
SELL	1q23-q25	Cell adhesion
SERPINE1	7q21.3-q22	'Bait' for tissue urokinase
SERPINF1	17p13.3	Inhibitor of angiogenesis.
SOD1	21q22.1; 21q22.11	Free radical
SOD2	6q25.3	Free radical
SORD	15q15.3	Polyol pathway
SP1	12q13.1	Transcription factor
SPARC	5q31.3-q32	Inhibits cell-cycle progression
SST	3q28	Peptide hormone
SUMO4	6q25	Ubiquitin-specific protease activity
TAB2	6q25.1	Phosphorylation
TCF4	18q21.1	Transcription factor
TIMP3	22q12.1-q13.2; 22q12.3	Catalytic zinc cofactor
TLR4	9q33.1	Receptor activity
TNC	9q33	Cell adhesion
TNF	6p21.3	Cell proliferation
TNFRSF13B	17p11.2	Humoral immunity
TNFSF4	1q25	Cytokine production
VASH1	14q24.3	Angiogenesis inhibitor
VCAM1	1p21.2	cell-cell recognition
VDR	12q13.11	Translation regulator
VEGFA	6p12	Vasculogenesis
VEPH1	3q24-q25	Unknown
VSTM2B	19q12	Unknown
ZNF238	1q44-qter	Transcription factor
